Megaloblastic Anemia associated with Jejunal Diverticula

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MEGALOBLASTIC ANEMIA in association with intestinal diverticula is a rare clinical entity but is being recognized with increasing frequency. Taylor[17] described a case of "pernicious anemia" associated with jejunal diverticulosis in 1930. Since then approximately 40 cases of megaloblastic anemia secondary to jejunal diverticula have been reported.* The following case illustrates the interesting features of this disorder and demonstrates the importance of establishing the correct diagnosis by means of the proper laboratory and radiologic studies.

Report of a Case

A 79-year-old Negro man was referred to Los Angeles County Harbor General Hospital on August 11, 1961, because of a 20-pound loss in weight in the preceding seven months and recent discovery that the hemoglobin content was 8.5 gm per 100 ml. For three months before admission he had had anorexia, nausea and "indigestion" with flatulence. On questioning, he said he had not had vomiting, hematemesis, jaundice, diarrhea, melena, gastrointestinal operations or previous treatment for anemia. He said that for eight years he had had numbness and tingling of the lower extremities. His diet had been poor in proteins but was otherwise not unusual. He had always been in good health and had never before been in hospital.

The only significant items in the past history were syphilis in 1918 and the finding of bilateral cataracts and macular degeneration at the Harbor General Hospital Eye Clinic in 1958.

On physical examination the patient appeared well developed, fairly well nourished and in no acute distress. The blood pressure, pulse and temperature were within normal limits. Arcus senilis and small cataracts were present bilaterally. There was no scleral icterus. On funduscopic examination bilateral macular degeneration was observed. There was an aneurysmal dilatation of the right common carotid artery. Minimal atrophy of the papillae of the tongue was noted. The lungs were clear to auscultation. The heart was slightly enlarged and there was a grade II aortic systolic murmur. The liver and spleen were not palpable. A small right inguinal hernia was present. There was no significant enlargement of lymph nodes. The prostate gland was slightly enlarged. Biceps and patellar reflexes were hypoactive bilaterally. There was decreased vibratory sensation over both lower extremities.

Erythrocytes numbered 1.9 million per cu mm and the proportion of reticulocytes was 1.9 per cent. Hemoglobin content was 6.7 gm per 100 ml and the hematocrit was 22.5 per cent. Leukocytes numbered 4,300 per cu mm with the cell differential within normal range. The red cell indices were: mean corpuscular volume 118 cubic microns, mean corpuscular hemoglobin 35 micromicrograms and mean corpuscular hemoglobin concentration 30 per cent. Microscopic examination of peripheral blood showed moderate macrocytosis, anisocytosis and poikilocytosis and some hypersegmented polymorphonuclear leukocytes. The platelets were adequate. The red blood cell arginase activity was 77 (normal is less than 46 mg of urea nitrogen liberated per 10^{11} erythrocytes per hour).[12] The serological test for syphilis was weakly reactive. Other studies included the following (per 100 ml): blood urea nitrogen 17 mg, fasting blood sugar 93 mg, uric acid 6.8 mg, serum calcium 8.6 mg, total proteins 6.9 gm (4.4 gm albumin and 2.5 gm globulin), cholesterol 210 mg, serum bilirubin 1.0 mg total with 0.8 mg indirect, serum carotene 78 micrograms and serum iron 80 micrograms with a total iron-binding capacity of 240 mcg. The acid phosphatase was 0.3 units. The urine was negative for glucose, protein and cells. The stool was soft, with no increased fat content, and was negative for occult blood, ova and parasites. A stool culture was negative for pathogenic organisms.

X-ray examination of the chest showed a right hilar mass, which most likely represented an ectatic aorta. Gastric analysis showed some free acid after histamine stimulation, but a similar study, however, six days later showed no free acid. Upper gastro-

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intestinal x-ray studies demonstrated multiple large duodenal and upper jejunal diverticula. The remainder of the small bowel was normal. No abnormality was noted in a barium enema examination. Bone marrow aspirate showed megaloblastic erythropoiesis and giant band forms and metamyelocytes. The intestinal absorption of radioiodinated triolein was 7 per cent (normal).

The patient was initially observed while on a regular hospital diet. Serial reticulocyte counts showed no significant response. Urinary excretion of radioactive vitamin B_{12} (Schilling test) was nil at first, then after administration of intrinsic factor the excretion was 2 per cent (normal 8 per cent or greater). After two courses of tetracycline therapy (500 mg four times a day from September 23 to October 6 and again October 21 to October 26) another Schilling test was performed on November 2, 1961, with a result of 8 per cent excretion (Table 1). At that time the patient was completely asymptomatic, had excellent appetite and had gained 15 pounds in weight. There was excellent reticulocyte response (26.8 per cent on the sixth day) to the cyancobalamin administered with the Schilling tests. At this time erythrocytes numbered 4.6 million per cu mm, hemoglobin content was 13.7 gm per 100 ml and the hematocrit 41 per cent. Thereafter the patient was observed regularly in the hematology clinic of the hospital, receiving monthly intramuscular injections of 100 micrograms of vitamin B_{12}. His hemogram remained within normal limits. A Schilling test two years later (August 19, 1963) was 0.4 per cent (Table 1).

TABLE 1.—*Urinary Excretion of Radioactive Vitamin B_{12} (Schilling Test)*

Date		*Per Cent excretion in urine in 24 hrs.**
Sept. 7, 1961....	Without intrinsic factor	0
Sept. 12, 1961..	With intrinsic factor	2.0
Nov. 2, 1961.....	After therapy with tetracycline	8.0
Aug. 19, 1963....	Without intrinsic factor	0.4

*Normal 24-hour urinary excretion of $Co^{57}B_{12}$ is greater than 8 per cent in this laboratory.

Comment

In this case the peripheral blood and the bone marrow were characteristic of megaloblastic anemia. The elevated arginase activity in the red blood cells was consistent with this diagnosis.[12] Among the many mechanisms causing megaloblastic anemia, practically all are due to deficiency of vitamin B_{12} or of folic acid or of both.[5] Two of the most common in the United States are pernicious anemia and idiopathic steatorrhea. In full-blooded Negroes, pernicious anemia although uncommon is not rare.[15] In the present case the results of the Schilling test with intrinsic factor and the presence of free acid in the gastric juice ruled out this diagnosis. The normal stools, absence of diarrhea, normal serum carotene, and normal radioiodinated triolein test[4,7,14] would make the diagnosis of idiopathic steatorrhea unlikely.

Repeated reticulocyte counts were done while the patient was on a regular hospital diet. Absence of significant reticulocyte response indicated that the anemia was most likely not simply due to dietary lack of vitamin B_{12} or of folic acid.

There was no history of ingestion of phenylbutazone or anticonvulsant drug, which may cause a megaloblastic anemia.[3,13] Megaloblastic change may occur in congenital and acquired hemolytic states such as hereditary spherocytosis, thalassemia, hemoglobinopathies, Coombs-positive hemolytic anemias and paroxysmal nocturnal hemoglobinuria.[9] With bilirubin content in normal range and an absence of reticulocytosis until cyanocobalamin was administered parenterally, there was no evidence of an overt hemolytic process in this patient. The normal results of the Schilling test after tetracycline and the absence of proteinuria excluded the possibility of a selective[10] or familial[6] malabsorption of vitamin B_{12}, which is probably due to a deficiency of a factor in the succus entericus.

The gastrointestinal x-ray studies revealed multiple large duodenal and jejunal diverticula. The studies also determined that there were no other gross pathological changes in the gastrointestinal tract such as strictures and blind loops. After broad spectrum antibiotic therapy with tetracycline, the patient's general condition and weight improved, anemia abated and the absorption of vitamin B_{12} was demonstrated to be normal by the Schilling test. The most likely mechanism for this improvement is that the tetracycline destroyed the intestinal bacteria responsible for impairing absorption of or utilizing the vitamin B_{12}.[7,16,18] The result of the Schilling test two years after the course of tetracycline therapy (0.4 per cent excretion) indicated that the effect of the treatment was, as expected, temporary. Thus, continued parenteral vitamin B_{12} therapy is necessary, as if the patient had pernicious anemia, although the underlying mechanism for the malabsorption of vitamin B_{12} of course is clearly different. Surgical resection of the diverticula might be effective,[1,11] but in this patient is not indicated. Intriguing, but unknown, factors are the duration of the diverticula and the causes for the apparent change in bacterial flora.

Summary

A case of megaloblastic anemia associated with duodenal and jejunal diverticula occurring in an

elderly Negro man is presented. Studies with radioactive vitamin B_{12} and gastrointestinal x-rays clearly established the diagnosis. Parenteral maintenance therapy with vitamin B_{12} is required as in pernicious anemia, although the pathophysiology of vitamin B_{12} absorption is different.

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ADDENDUM: After this manuscript was submitted, a similar case in an 83-year-old Caucasian man was studied.

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